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(54) Title: STABLE ANHYDROUS FORMULATION

(57) Abstract

The present invention is a cosmetic or pharmaceutical composition for topical application comprising a silicone gel and an effective amount of a biological active, especially a retinoid. The compositions permit stabilization of the biologically active agents.

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STABLE ANHYDROUS FORMULATION

Field of the Invention

The present invention relates to cosmetic or pharmaceutical compositions comprising stable active agents. In particular, the invention relates to compositions in which active agents are stabilized by incorporation into a silicone gel.

Background of the Invention

In recent times, cosmetics have become developed beyond the concept of mere ornamentation for the face. Consumers now demand more from their makeup than simple color, coverage or moisturizing: it is now preferred that cosmetics provide some benefit to the skin, rather than just decorating it or making it feel softer. This consumer preference has resulted in the frequent use of biologically active ingredients, in many cosmetic products. In view of the now well-recognized damaging effects of sun exposure on the skin, particularly favored active components are those which can counteract or prevent those effects. These components include, for example, sunscreens, antioxidants, and anti-wrinkle agents.

One of the primary difficulties in employing actives in a formulation is the potential instability of the active once incorporated. The very reason for their use in the formulation, i.e., their biological activity, means that they are not inert, and are therefore potentially subject to reduction or loss of potency if not combined with the proper vehicle. A number of routinely encountered factors can readily inactivate a biologically active compound in a formulation before it even reaches the consumer. Such factors include, for example, oxygen, extreme temperatures,

UV light, water, and lipid peroxidases. It is particularly difficult to avoid the effects of oxygen and UV light, which are of course virtually ubiquitous in nature. Although water can technically be avoided by anhydrous formulation, many of the very desirable actives are water soluble, making their incorporation into an anhydrous formulation problematic. Thus, there continues to be a need for development of a cosmetically acceptable vehicle which will be capable of readily incorporating water soluble actives, yet will protect the actives from environmental factors which rob them of their biological activity. The present invention provides a solution to this continuing problem.

Summary of the Invention

The present invention provides an anhydrous cosmetic or pharmaceutical formulation for topical application to the skin, the formulation comprising a silicone gel, in combination with a safe and effective amount of one or more biologically active components. The invention also comprises a method of stabilizing a biologically active component, the method comprising combining the active component with a stabilizing amount of a silicone gel. A preferred active component is a retinoid.

In a preferred embodiment, the formulation also comprises an effective amount of an oil soluble antioxidant.

Detailed Description of the Invention

It has now been unexpectedly discovered that it is possible to stabilize biologically active materials by their combination with a silicone gel. The gels employed in the present invention comprise a vehicle in which an organopolysiloxane elastomer is dispersed. The vehicle can comprise any cosmetically acceptable silicone oil, or a combination of silicone oils. The silicone oil may be any

volatile or non-volatile silicone oil, for example, any methylated linear or cyclic non-elastomeric organopolysiloxane, or combinations thereof. Preferably, however, the vehicle is a lower molecular weight dimethicone, trimethicone, cyclomethicone, or a mixture of such oils. Preferred silicone oils useful as the gel vehicle in the present invention include, but are not limited to, phenyl trimethicone, or methylated cyclic organopolysiloxanes having ring sizes from 4 to 12, such as octamethylcyclotetrasiloxane or decamethylpentasiloxane.

The gel is prepared by dispersing in the vehicle an organopolysiloxane elastomer. An elastomer is generally a chain polymer having a degree of cross-linking sufficient to provide a rubber-like material. In the present gel, the elastomer is an at least partially crosslinked or at least partially cured hetero-chain elastomer. Particularly preferred are those which are at least partially cured addition reaction products, i.e., hydrosilation products, or addition polymerization products, of an organopolysiloxane having unsaturated groups, such as vinyl or allyl, preferably bonded to at least one terminal silicon atom, and another silicone compound capable of participation in the addition reaction, such as an organohydrogenpolysiloxane. Suitable organopolysiloxane elastomers, having a three-dimensional cross-linked structure, are described, for example, in US Patent No. 5,266,321, the contents of which are incorporated herein by reference. However, other suitable elastomer materials are disclosed in, for example, US Patent Nos. 4,980,167 and 4,742,142.

A preferred organopolysiloxane is one which is at least partially crosslinked, or is an at least partially cured hetero-chain elastomer. In one preferred embodiment, the organopolysiloxane elastomer is one which is one which is an

at least partially cured addition reaction products, i.e., hydrosilation products, or addition polymerization products, of an organopolysiloxane having unsaturated groups, such as vinyl or allyl, preferably bonded to at least one terminal Si atom, and another silicon compound capable of participation in the addition reaction, such as an organohydrogen polysiloxane.

The chosen elastomer is dispersed in the vehicle by known homogenization techniques. The elastomer dispersed in the vehicle provides a soft, stable viscous gel, or gel-like material. Alternatively, the gel can be purchased premade, with the elastomer already dispersed in the vehicle. Such products are available under the name Gransil, for example Gransil GCM or Gransil PM, from Grant Industries, Inc., Elmwood Park, New Jersey. The amounts of elastomer and vehicle may vary, depending on the desired viscosity, but generally should be in the range of 5-40% elastomer and 60-95% vehicle.

The gel so prepared can be directly combined with the desired active agent. In a preferred embodiment, the active agent is a retinoid, e.g., Vitamin A(retinol), Vitamin A aldehyde(retinal), Vitamin A acid(retinoic acid) and derivatives of these compounds, for example, retinyl palmitate, retinyl acetate and the like. Retinoids are readily miscible with the silicone gel, and can be mixed directly into the gel, or as dissolved in an oil-miscible solvent. The retinoid is added to the gel in an amount sufficient to produce about 0.001-5%, more preferably about 0.01-2%, concentration by weight of the total composition to be applied. Although retinoids, especially retinol, are particularly preferred active agents to be stabilized by this method, it will be readily recognized by the skilled artisan that other active agents, such as Vitamin E and derivatives, long-chain alpha hydroxy acids, ceramides, or

skin lipids to enhance barrier function can also benefit from combination with a silicone gel.

In addition to the oil-soluble or lipophilic active agents, however, it has surprisingly been discovered that the silicone gel system can also serve to stabilize water-soluble actives. Although not soluble in the silicone gel, it is possible to simply disperse the water-soluble active in the gel, and thereby provide the stabilizing effect which also protects the oil-soluble active. In a preferred embodiment, the water-soluble active is Vitamin C, or a water-soluble derivative thereof, which has useful cosmetic/dermatological properties, such as stimulating collagen synthesis, but which is generally very unstable in formulation. Other useful water-soluble actives which can also be employed are, for example, water soluble preservatives and antioxidants; skin conditioning agents, for example, humectants, such as hyaluronic acid salts, hydrogels, or glycerol or elastin; collagen; alpha-and beta-hydroxy acids; or milk protein. In a preferred embodiment of this invention, the composition comprises at least one oil soluble active and at least one water soluble active. In a particularly preferred embodiment, the composition comprises the combination of retinol with Vitamin C, which has many benefits to the skin, including collagen stimulation, the Vitamin C being present in an amount of from about 0.1-20% by weight of the total composition.

Although the gel itself is sufficient to stabilize a susceptible active agent against oxygen degradation, it may be desirable to supplement this property with one or more additional antioxidants, preferably lipophilic antioxidants. Examples of useful antioxidants include Vitamin E and its derivatives, BHT, BHA, NDGA, propyl gallate, and the like. In a preferred embodiment, the antioxidant employed is an

oil extract of green tea, this type of extract being more stable than aqueous green tea extracts. The oil soluble green tea extract is employed in an amount of from about 0.01-15% by weight of the total composition.

Additional components may also be added to the composition, depending upon the intended use of the final product. Examples of such additional components may include, but are not limited to, sunscreens, fragrance, preservatives, emollients, viscosity modifying agents, pigments, and dispersants. The active-containing silicone gel composition can be used as is, or can be further diluted by combination with an appropriate solvent or vehicle, to achieve the desired consistency for application. The vehicle or solvent may be any anhydrous base in which the silicone gel composition is compatible and miscible. Examples of appropriate bases are volatile or non volatile oils. Suitable volatile oils include cyclic and linear silicones, such as cyclomethicone, octamethylcyclotetrasiloxane, and decamethylcyclopentasiloxane; or straight or branched chain hydrocarbons having from 8-20 carbon atoms, such as decane, dodecane, tridecane, tetradecane, and C8-20 isoparaffins. Suitable non-volatile oils include vegetable oils, carboxylic acid esters, animal oils, glyceryl esters, non-volatile silicones, and nonvolatile hydrocarbons. Particularly preferred are the volatile cyclic silicones. It is desirable in many cases, however, to retain much of the gel-like consistency of the original composition; therefore, in such a composition, the added base is preferably used in an amount of no more than about 10-15% of the total weight of the composition.

The preferred composition of the present invention is one in which the active component is a retinoid, and most preferably, one in which the retinoid is retinol. These

compounds have a number of useful skin-enhancing activities, such as treatment of the symptoms of intrinsic aging, e.g., lines and wrinkles, improvement of skin texture and appearance, prevention or treatment of the symptoms of photoaging, and acne treatment. However, they are extremely susceptible to degradation by a number of external sources, thereby creating significant difficulties in formulating them in such a way as to retain their activity, and to permit the formulations to retain activity over a prolonged storage period. The present retinoid compositions, however, eliminate the need for special formulating conditions, such as dark rooms, nitrogen purging, or separate packaging of the active agent and the vehicle. In preparing the present compositions, the components are simply mixed together under standard conditions. The compositions so prepared show a remarkable stability over time, with the retention of at least about 85%, and preferably at least about 90% of the original activity, after a storage period of 8 weeks at room temperature, and as much as 80% or more retained activity even when stored at elevated temperatures(40°C) for 8 weeks.

The present invention will be further illustrated by the following non-limiting examples.

Example I

A composition of the invention is prepared as follows:

Materials	Weight %
Phase I	
Gransil PM-gel(Grant Industries)	85.00*
Phase II	
green tea oil extract(LipoChemical)	9.90
retinol 50P base(BASF)	0.10**

Phase III		
Ascorbic acid	USC-FCC	5.00

*comprising phenyltrimethicone(70%) and organopolysiloxane(30%)
**50% solution in Tween 20

Preparation:

Phase I is weighed into a primary mixing kettle. In an auxiliary kettle, the Phase II components are mixed under propeller mixer agitation until the solids are completely dissolved; the mixture at this point is slightly cloudy. The phase III component is then sprinkled over the Phase II materials, while mixing under propeller mixer agitation. The uniform dispersion of the combined Phases II and III is confirmed by placing a small sample between glass slides and checking for undispersed ascorbic acid. When the combined Phases II and III are well-dispersed, they are added to Phase I in the primary mixing kettle under mixer agitation, until the combined phases are uniform. The mixture is removed from the kettle through a nylon mesh filter bag, and stored in polyethylene-lined storage containers.

Example II

Compositions prepared according to Example I are then evaluated for their ability to retain activity over a variety of time and temperature storage conditions. In the first instance, the amount of retinol in the compositions is determined, by HPLC, shortly after preparation, and at intervals for up to 8 weeks thereafter, at temperatures of 4°C, 25°C, and 40°C. The results, showing amount of retinol activity remaining, are shown in Table I.

Table I

	Temperature of Storage		
Time Point	4°C	25°C	40°C
Initial	0.042%	0.042%	0.042%
1 week	0.038%	0.037%	0.036%
2 weeks	0.039%	0.039%	0.038%
4 weeks	0.039%	0.038%	0.034%
8 weeks	0.041%	0.040%	0.034%

These results show that at low and room temperature conditions, the compositions can retain up to about 90% or more activity after 8 weeks of storage, and even under extreme heat conditions, retains up to about 80% of its initial activity, thereby demonstrating the stabilizing effect of the silicone gel on retinol activity.

The stability of the ascorbic acid in the composition is also evaluated at 4°C, 25°C, and 40°C. At the end of eight weeks of storage, the compositions show 99%, 96% and 95% retention of ascorbic acid activity, indicating a high level of stabilization of this water-soluble active, even in a non-aqueous formulation.

What we claim is:

1. A cosmetic or pharmaceutical composition for topical application comprising a silicone gel and an effective amount of a retinoid.

2. The composition of claim 1 wherein the gel comprises an organopolysiloxane elastomer and a silicone oil vehicle.

3. The composition of claim 2 in which the elastomer is a reaction product of an organopolysiloxane having an unsaturated group bound to a terminal Si-atom and an organohydrogensiloxane, which reaction product is at least partially cured.

4. The composition of claim 2 in which the silicone oil is a low molecular weight dimethicone, trimethicone, or cyclomethicone.

5. The composition of claim 4 in which the silicone oil is phenyltrimethicone, or octamethylcyclotetrasiloxane.

6. The composition of claim 1 wherein the retinoid is retinol.

7. The composition of claim 1 which also comprises at least one antioxidant.

8. The composition of claim 7 wherein the antioxidant is an oil extract of green tea.

9. The composition of claim 1 which also comprises an effective amount of Vitamin C or a derivative thereof.

10. A cosmetic or pharmaceutical composition for topical application comprising a silicone gel, the gel comprising a (a) an organopolysiloxane elastomer which is a reaction product of an organopolysiloxane having an unsaturated group bound to a terminal Si-atom and an organohydrogensiloxane which reaction product is at least partially cured and (b)a silicone oil selected from the group consisting of a low molecular weight dimethicone, a trimethicone, or a cyclomethicone, combined with (c) an effective amount of a retinoid.

11. The composition of claim 10 wherein the retinoid is retinol.

12. The composition of claim 11 which also comprises an antioxidant.

13. The composition of claim 12 in which the antioxidant is an oil extract of green tea.

14. The composition of claim 10 which also comprises Vitamin C or a derivative thereof.

15. The composition of claim 10 which comprises retinol, an antioxidant, and Vitamin C or a derivative thereof.

16. The composition of claim 15 wherein the silicone oil is phenytrimethicone.

17. The composition of claim 15 wherein the silicone oil is octamethylcyclotetrasiloxane.

18. A method of stabilizing a retinoid which comprises mixing the retinoid with a silicone gel comprising an organopolysiloxane elastomer and a silicone oil vehicle.

19. The method of claim 18 wherein the elastomer is a reaction product of an organopolysiloxane having an unsaturated group bound to a terminal Si-atom and an organohydrogensiloxane which reaction product is at least partially cured.

20. The method of claim 18 wherein the silicone oil is a low molecular weight dimethicone, trimethicone, or cyclomethicone.

21. The method of claim 4 wherein the silicone oil is phenyltrimethicone, or octamethylcyclotetrasiloxane.

22. The method of claim 18 wherein the retinoid is retinol.

23. The method of claim 18 wherein the retinoid and silicone gel are also mixed with an antioxidant.

24. The method of claim 23 wherein the antioxidant is an oil extract of green tea.

25. A method of stabilizing a biologically active agent in a cosmetic or pharmaceutical composition which comprises mixing the agent with a silicone gel comprising an organopolysiloxane elastomer and a silicone oil vehicle.

26. The method of claim 25 wherein the silicone oil is a low molecular weight dimethicone, trimethicone or cyclomethicone.

27. The method of claim 26 wherein the silicone oil is phenyltrimethicone.

28. The method of claim 26 wherein the silicone oil is octamethylcyclotetrasiloxane.

29. The method of claim 25 wherein the composition also comprises an oil extract of green tea.

30. The method of claim 25 wherein the active agent is Vitamin C, or a derivative thereof.

31. A cosmetic or pharmaceutical composition comprising a water soluble biological active, wherein the active is stabilized in the composition by combination with a silicone gel comprising an organopolysiloxane elastomer and a silicone oil vehicle.

32. The composition of claim 15 which is anhydrous.

33. The composition of claim 15 wherein the active is Vitamin C.

34. A method of preventing or treating the symptoms of intrinsic aging or photoaging on the skin which comprises applying to the skin a composition of claim 1.

35. A method of preventing or treating the symptoms of intrinsic aging or photoaging on the skin which comprises applying to the skin a composition of claim 9.

36. A method of preventing or treating the symptoms of intrinsic aging or photoaging on the skin which comprises applying to the skin a composition of claim 10.

37. A method of preventing or treating the symptoms of intrinsic aging or photoaging on the skin which comprises applying to the skin a composition of claim 15.

38. A method of improving the texture or appearance of the skin which comprises applying to the skin a composition of claim 1.

39. A method of improving the texture or appearance of the skin which comprises applying to the skin a composition of claim 9.

40. A method of improving the texture or appearance of the skin which comprises applying to the skin a composition of claim 10.

41. A method of improving the texture or appearance of the skin which comprises applying to the skin a composition of claim 15.

INTERNATIONAL SEARCH REPORT

	National Application No
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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 790 055 A (L'OREAL) 20 August 1997 see page 3, line 14 - line 5; claims 1-14	1-40
A,P	WO 98 00105 A (UNILEVER) 8 January 1998 see the whole document	1-40
A,P	WO 98 00103 A (UNILEVER) 8 January 1998 see the whole document	1-40
A	EP 0 742 005 A (UNILEVER) 13 November 1996 see example 14	1-40
A	FR 2 732 595 A (L'OREAL) 11 October 1996 see the whole document	1-40
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

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